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Syntheses and Applications of Enantiopure δ-Amino Acids and their Precursors

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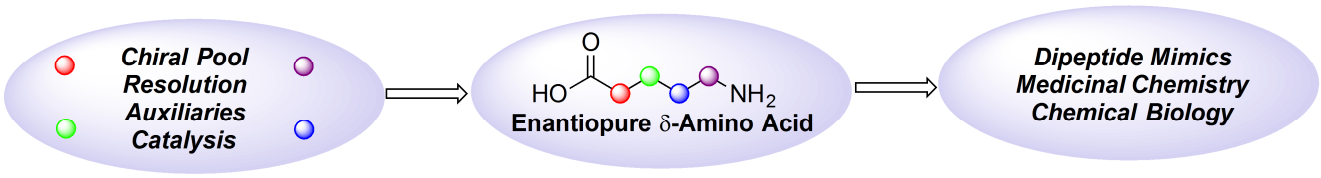

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Syntheses and Applications of Enantiopure δ-Amino Acids and their Precursors

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In recognition of the astonishing accomplishments and contributions to chemistry of Professor Sir Derek H. R. Barton FRS FRSE

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ABSTRACT

Enantiopure unnatural homologated amino acids, whereby there is >1 carbon atom between the C- and N- termini have found great utility in a number of applications. The enantiopure syntheses of β-amino acids are well documented, as increasingly are those of γ-amino acids. δ-Amino acids on the other hand are much less well-studied despite reports of their potential utility. This review attempts to summarise strategies that have been adopted towards the enantioselective synthesis of δ-amino acids and their precursors (e.g. nitrile/nitro/azido/ester/alcohol etc) and where appropriate demonstrate their utility. Only systems which are all carbon between the two termini are considered and only those where the shortest route between any given *C*-termini and any given *N*-termini is four carbons long (*i.e.* lysine derivatives are not considered).

1. Introduction

Unnatural peptidic amino acids (Figure 1a) have unsurprisingly been the subject of vigorous study for a very long time. For obvious reasons, their similarity to native amino acids mean that they can participate in a range of biological interactions either as discrete molecules in themselves, or as a part of an unnatural peptide. Unnatural α-Amino acids are, as one might expect, the largest representative class of molecule in this area,[1] but in more recent years β- and γ-amino acids have become of increasing interest. A major reason for the lag in the number of reports for these homologated systems is the difficulty in accessing stereogenically pure frameworks – the importance of such purity is of course self-evident. The stereoselective synthesis of β-amino acids and γ-amino acids have been the subject of other reviews which also detail their applications,[2,3] and we ourselves have contributed to the latter.[4] δ-Amino acids on the other hand have not had the same level of scrutiny, which is somewhat surprising given that they are essentially dipeptide mimics (Figure 1b). This review therefore seeks to examine the methods that have been employed towards their stereoselective synthesis and to highlight some of their notable applications.[3b] For the purposes of simplicity, only systems whereby there are no fewer than four *carbon* atoms between the *C*- and *N*-termini (or their immediate precursors) within the shortest route are considered. The nomenclature used is as per convention whereby the superscripted number(s) after the "δ" describe the positions of substitution (Figure 1c).

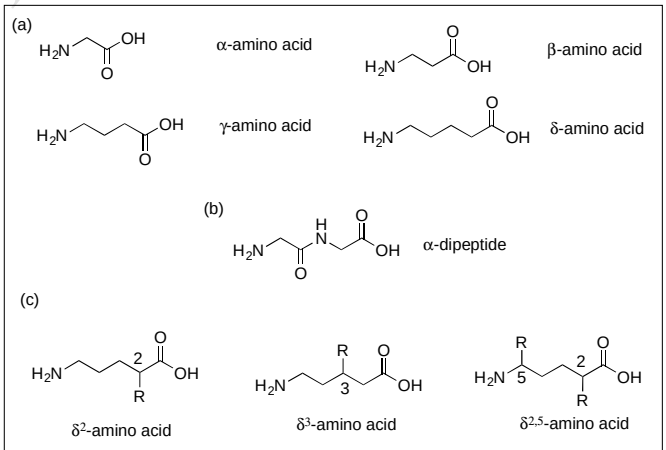
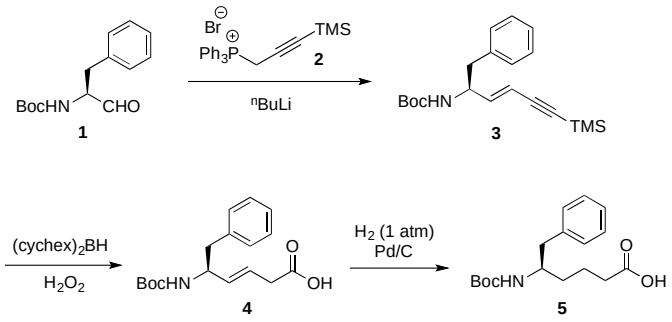


Figure 1 : (a) An α-amino acid and homologated variants (b) An α-dipeptide has the same number of atoms between the two termini as a monomeric δ-amino acid (c) A brief guide to the simple nomenclature of homologated amino acids

2. Synthesis *via* Chiral Pool Molecules

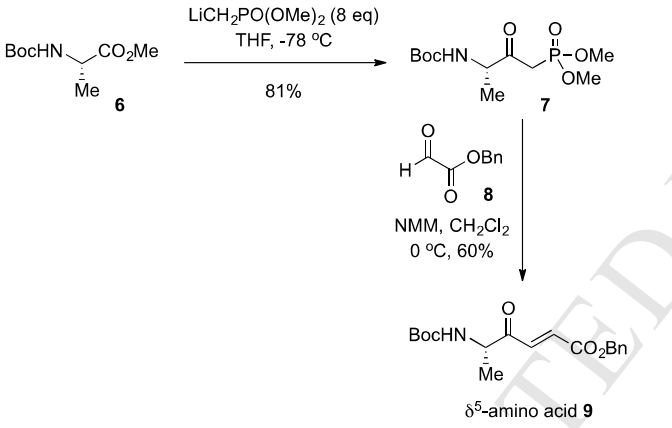
Perhaps the most obvious way to synthesize extended amino acids is to homologate existing stereogenically pure systems – normally the corresponding α-amino acid. An early example of this came from the group of Kaltenbronn who were developing a range of renin inhibitors containing dipeptide mimetics.[5] Starting from the amino acid derived aldehyde **1**, homologation using Wittig reagent **2** gave a separable mixture of alkenes **3**. Subsequent selective hydroboration of the alkyne in this system

followed by reduction gave the Boc-protected δ^5-amino acid **5** (Scheme 1).



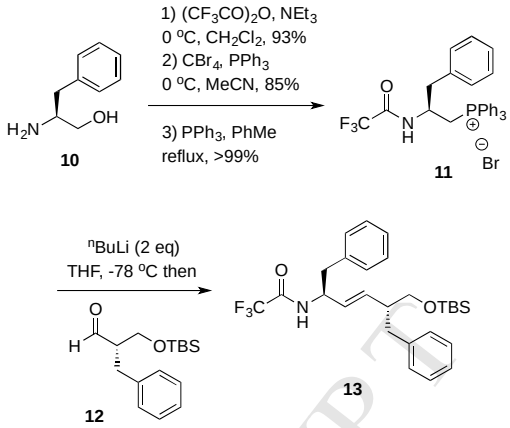
Scheme 1 : Kaltenbronn's δ^5-amino acid synthesis *via* homolgation of an α-amino acid derived aldehyde

Another example of this type of homologation approach comes from the work of Déziel and co-workers who accessed a range of δ-amino acids by homologation of the corresponding α-amino acids.[6] This was achieved through conversion of the methyl ester protected C-terminus into the corresponding β-ketophosphonate **7** which could then undergo Horner-Wadsworth-Emmons reaction with benzylglyoxylate **8** to give the protected δ^5-amino acid **9** (Scheme 2).



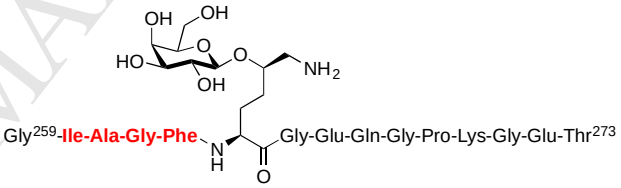
Scheme 2 : Deziel's synthesis of a δ^5-amino acid analogue of alanine

A similar approach was taken by Luthman and co-worker in their synthesis of δ-amino acid systems with two stereogenic centres (Scheme 3).[7] In this work, they synthesized phosphonium salt **11** in three steps from (*S*)-phenylalinol **10** in overall 92% yield. The next Wittig stage was performed using (*R*)- or (*S*)-**12**, as access to both epimers was required. However, the enantiomeric purity of the aldehydes used was only 82 and 84% for (*R*)- and (*S*)-enantiomers respectively as they were accessed using either lipase-catalysed desymmetrisation or resolution as key steps (see section 3), meaning that the diastereomeric purity of the final δ-amino acids was compromised.



Scheme 3 : Luthman's synthesis of a $\delta^{2,5}$-amino acid dipeptidomimetic with two stereocentres

Nevertheless, both Déziel and Luthman's homologation approaches were used to good effect by Linusson and Kihlberg who developed a range of isosteric glycopeptides aimed at investigating the binding of the CII259-270 glycopeptide **14** to the arthritis-associated murine A^q class II major histocompatibility complex (MHC) protein.[8] In this study, the authors wished to investigate the effect of removing hydrogen-bonding possibilities from the glycopeptide on binding. They achieved this by using δ-amino acids to strategically replace various dipeptide units within the glycopeptide (Figure 2).

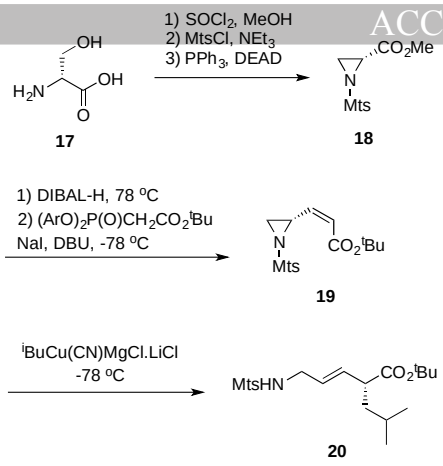


Glycopeptide **14** (CII259-273)

a : R^1 = ^{i}Bu, R^2 = Me
b : R^1 =Me, R^2 = H
c : R^1 = H, R^2 = Bn

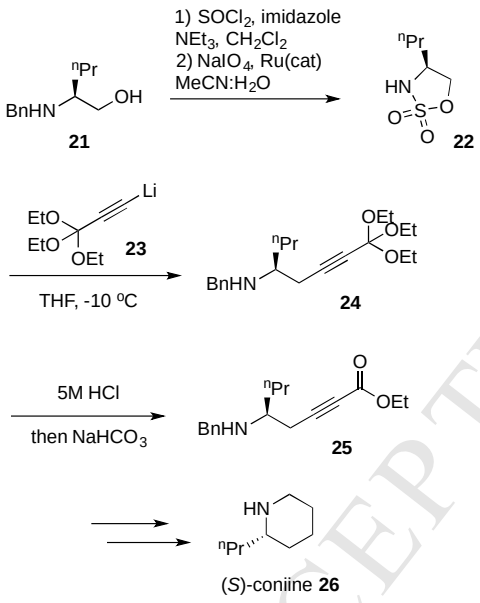
Figure 2 : Glycopeptide **14** with the amino acids targeted for dipeptide bioisosteric replacement highlighted

Based on several earlier studies by Yamamoto, Taga, Ibuka and Fujii,[9] alongside work by Wipf,[10] another Wadsworth-Emmons homologation approach was utilised by Fujii himself and co-workers in their investigation of dipeptide isosteres aimed at developing agonists of GPR54 a Gq-protein-coupled receptor linked to antimetastatic activity.[11] Access to the δ^2-amino acid **20** itself was achieved through the stereoselective copper mediated *anti*-S_N2' ring-opening of an aziridine which was derived from D-serine **17** (Scheme 4).[9a,10]



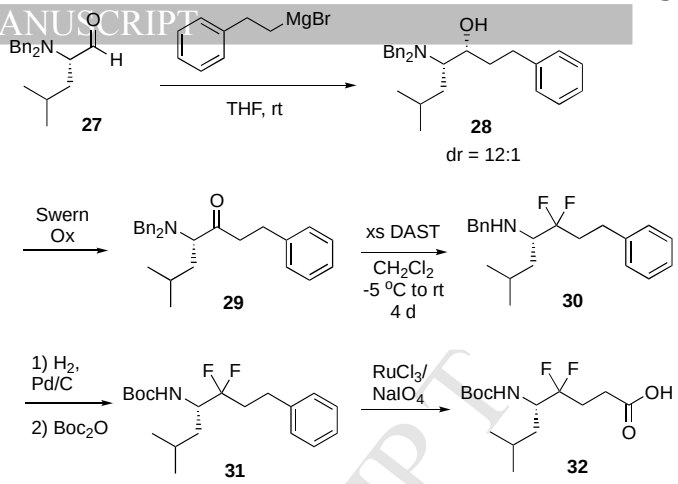
Scheme 4 : Fujii's synthesis of a dipeptide analogue aimed at GPR54 agonism

A different homologation of α-amino acids was used by Eskici and co-workers in the formal synthesis of (*S*)-coniine **26**, who converted L-norvaline derived β-amino alcohol **21** into the corresponding cyclic sulfamidate **22**.[12] This underwent reaction with lithium acetylide **23** to generate intermediate orthoester **24**, which under acidic conditions gave δ[5]-amino ester **25**. Thereafter, (*S*)-coniine was obtained over a few simple steps (Scheme 5).



Scheme 5 : Eskici's synthesis of (*S*)-coniine **26** *via* a δ[5]-amino ester

Seebach and co-workers utilized a Grignard homologation process in their synthesis of *gem*-difluoro dipeptide isosteres (Scheme 6).[13] Starting with homovaline derivative **27**, the aforementioned Grignard reaction with 2-phenylethyl magnesium bromide gave the non-chelation controlled β-amino alcohol in a 12:1 dr. Swern oxidation to the ketone followed by DAST fluorination gave the *gem*-difluoro compound **30**. Interestingly, during this procedure the DAST also removed one of the benzyl groups, which the authors suggest occurs *via* an aziridinium intermediate followed by S_N2 displacement of one of the benzyl groups. The authors then incorporated this dipeptidomimetic into angiotensin analogue **33** to give mimetic **34** in an attempt to find a renin inhibitor (Figure 3). Although no inhibition was observed, this was the only peptide to be tested, and further investigations are worthy of attention.



Scheme 6 : Seebach's *gem*-difluoro-δ[5]-amino acid synthesis

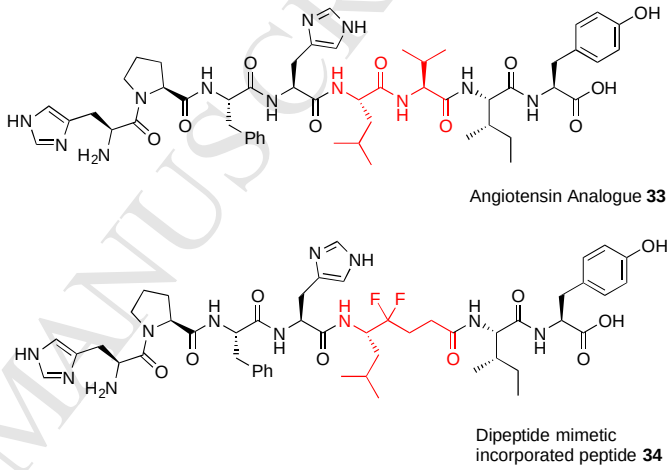


Figure 3 : Seebach's peptidomimetic of an angiotensin analogue

δ-Amino acids derived from sugars have also been reported. For example, Kessler and co-workers[14] used the glucosamine derived δ-amino acid **35** (first synthesized by Heyns and Paulsen[15]) as a D-Ser-Ser mimic (Figure 4).

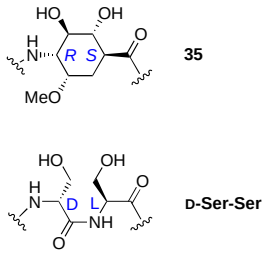
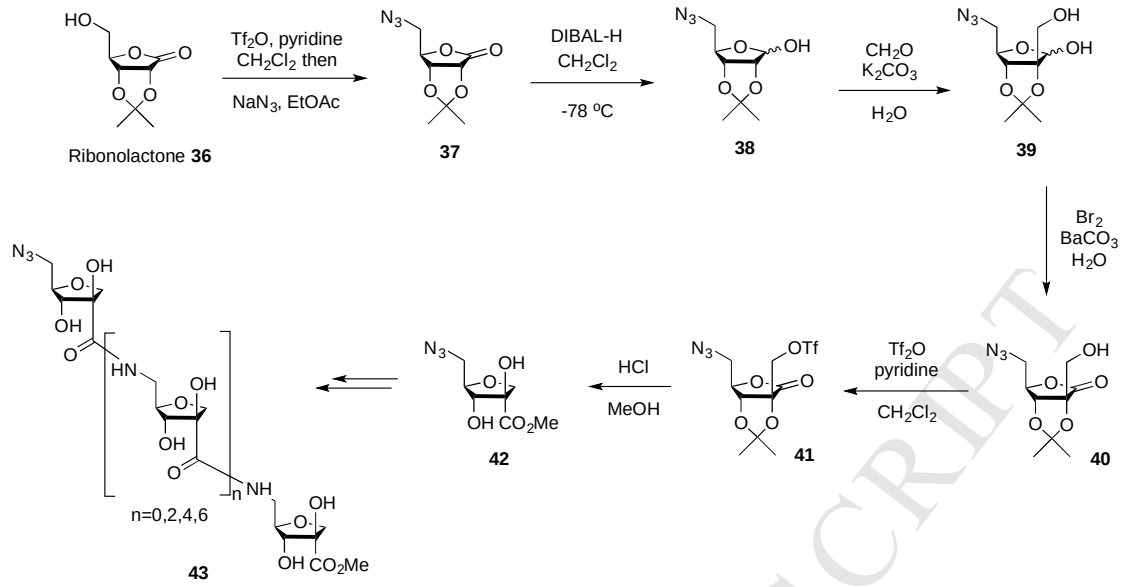


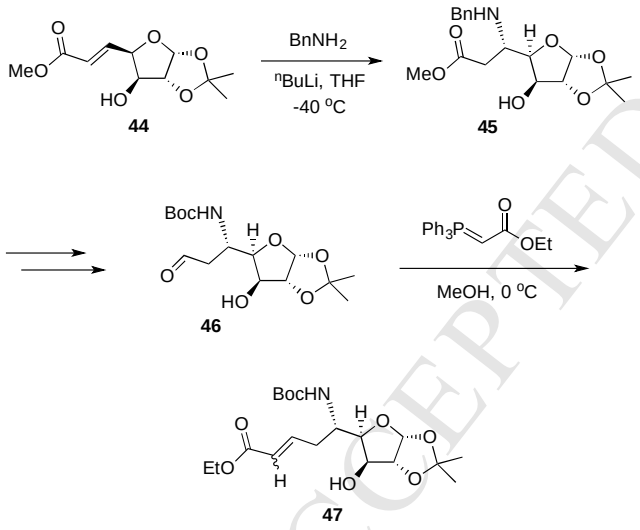
Figure 4 : Kessler and co-workers have shown that glucosamine derived amino acids **35** has a similar conformation to a D-Ser-Ser dipeptide and as such is a good mimic for it.

δ-Ribose derived δ-amino acids were developed by Fleet and co-workers towards the attempted synthesis of foldamers.[16] Described as a "branched-δ-THF", these systems were synthesized from the protected D-ribonolactone **36** by S_N2 displacement with azide – the precursor to the N-terminus. Reduction of this compound to the lactol, followed by aldol reaction with formaldehyde and selective oxidation of hemiacetyl hydroxyl introduced the 2'-hydroxymethyl substituted system **40**. Treatment with HCl and methanol removed the acetal and formed the methyl ester along with cyclization onto the triflate by the resulting secondary alcohol to give **42**. This was then used to form the unnatural δ-peptide **43**.



Scheme 7 : Fleet's D-ribose derived δ-amino acid and corresponding foldamer

Sharma and co-workers have also utilized carbohydrate derived systems as frameworks for δ-amino acids.[17] In this work, homologation of aminosugar **45** – itself synthesized by a Michael addition of benzylamine to conjugated ester **44**[18] gave unsaturated δ^5 amino acid **47**. These systems were then utilized in the study of α/δ-hybrid peptides as novel foldamers.[19]

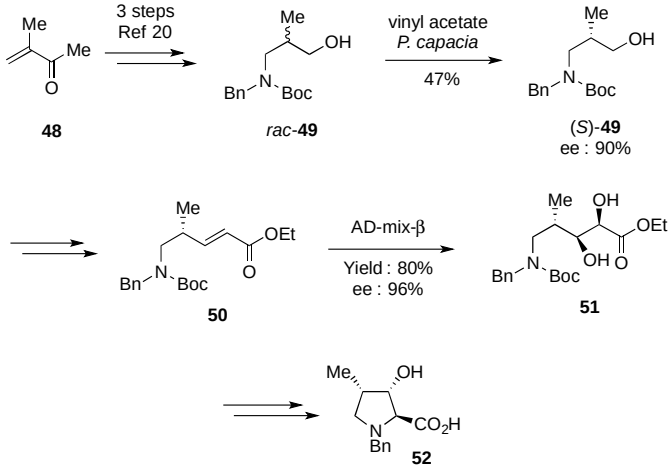


Scheme 8 : Sharma and coworkers' access to a carbohydrate δ-amino acid, accessed by homologation of a β-amino acid

3. Synthesis *via* Resolution Methods

An alternative method of accessing enantiopure δ-Amino Acids is to resolve the desired enantiomer from a racemic mixture formed at some stage in the synthesis. This can be achieved through either kinetic (relying on the different chemical properties of racemic starting materials) or chiral (relying on the different physical properties of diastereomeric products) resolution.

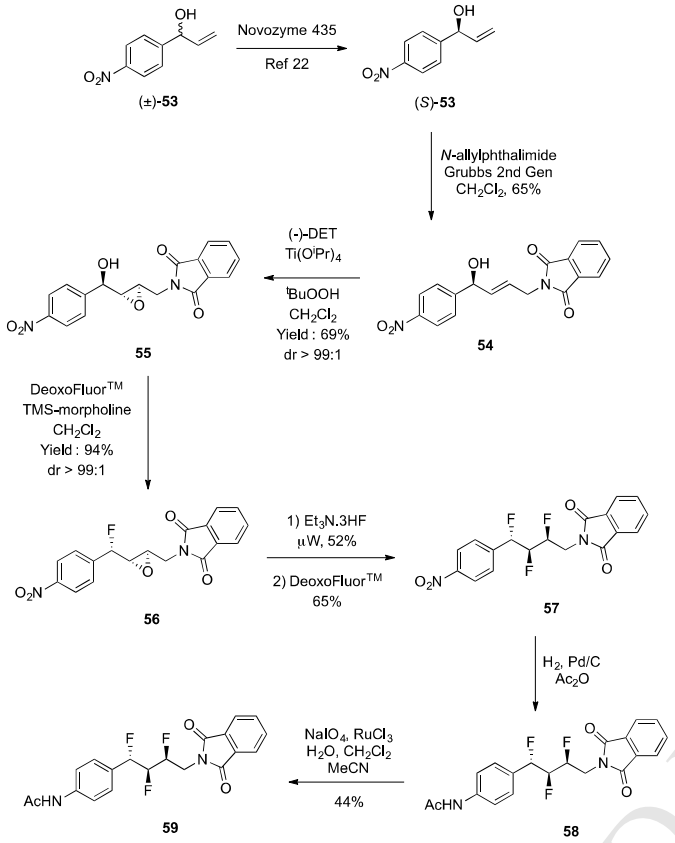
As an example of the former, Mantelingi, Rangappa and co-workers have made a range of proline derivatives via a δ-amino acid precursors.[20] The first stereocentre was installed *via* an enzymic resolution of a racemic γ-aminoalcohol (±)-**49**, itself made from methyl methacrylate **48** (Scheme 9). This was achieved using *Pseudomonas capacia* in the presence of vinyl acetate to generate the desired intermediate (*S*)-**49** with 90% enantiomeric excess. Homologation by oxidation and Wittig reactions (as used in the approaches above), gave the corresponding δ-amino acid precursor **50**. This system was further functionalized by a catalytic dihydroxylation to generate the vicinal diol **51** in an 80% yield and an enantiomeric excess of 96% before ultimately being converted to the desired proline derivative **52**.



Scheme 9 : Mantelingi and Rangappa's synthesis of proline derivatives proceeds via a δ-amino acid where the initial stereocentre is installed by an enzymic kinetic resolution

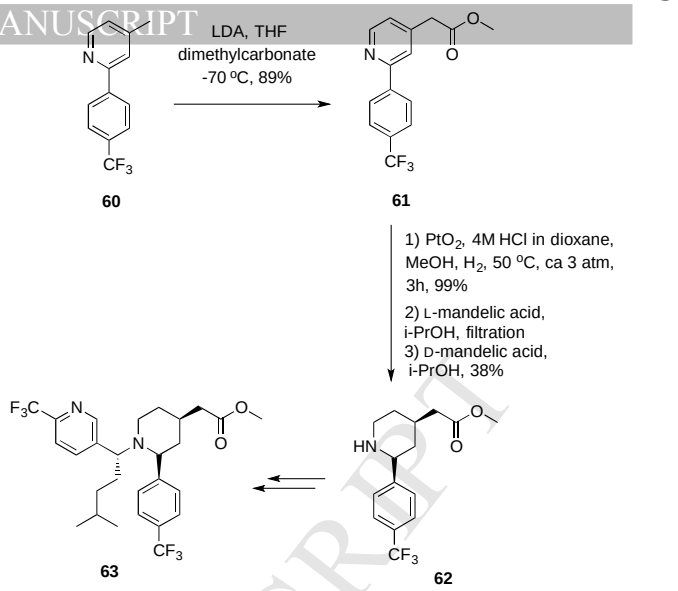
Similarly, Hunter and co-workers made protected α,β,γ-trifluoro-δ-amino acid **59**[21] by first using the highly reactive polymer supported lipase Novozyme 435 according to the work of Kočovský and co-workers[22] to resolve an aryl allylic alcohol **53**. The resulting enantiopure system was homologated by cross metathesis with *N*-allylphthalimide using Grubbs 2nd generation catalyst to give the δ-amino acid precursor **54** (Scheme 10). As with the above example subsequent stereocentres were introduced using a catalytic asymmetric process. In this case a Sharpless Asymmetric Epoxidation gave the resulting epoxide in 94% yield and >99:1 dr. Fluorination with bis(2-

methyoxyethyl)amino sulfur trifluoride (DeoxyFluor) gave compound **56** in 94% yield and >99:1 dr. Treatment of this with neat trimethylamine trihydrofluoride under microwave conditions and a second treatment with DeoxyFluor gave the trifluoro compound **57**. The *C*-terminus was generated by the oxidative degradation of the aromatic ring to give the desired δ-amino acid precursor **59**.



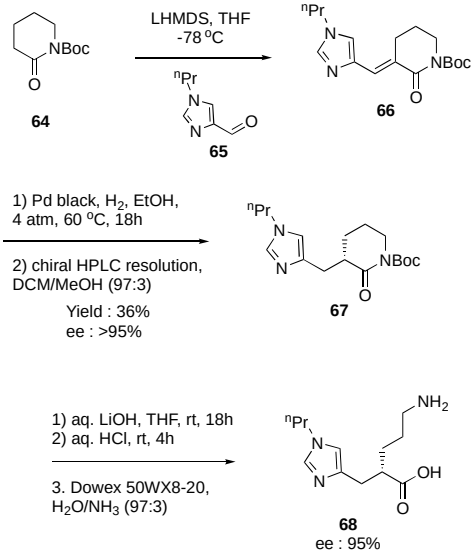
Scheme 10 : Hunter and co-workers' fluorinated δ-amino acid synthesis begins with an enzymic resolution

A prominent example of *chiral resolution* was given by Hall and co-workers in the synthesis of piperidine-derived γ-secretase modulators - compounds with therapeutic potential for the treatment of Alzheimer's disease.[23] In this work, deprotonation of pyridine **60** and trapping with dimethylcarbonate gave ester **61**. Subsequent reduction of this gave the racemic *cis*-piperidine. Chiral resolution – conducted first by crystallisation with L-mandelic acid where the formed salt (containing the unwanted piperidine enantiomer) was filtered off, followed by crystallisation from the filtrate using D-mandelic acid gave the desired enantiomerically pure piperidine **62**, the absolute configuration of which was confirmed *via* X-ray crystallographic analysis. With the required stereochemistry now in place, the successful synthesis of target compound **63** completed in a total of 7 steps (Scheme 11).



Scheme 11 : Hall's chiral resolution *via* crystallisation of a piperidine ester aimed at the treatment of Alzheimer's

Chiral resolution was also utilised by Mark Bunnage and his co-workers at Pfizer in the synthesis of a series of novel imidazolepropionic acids - compounds that were projected to possess antithrombotic potential.[24] In this approach, Boc-protected piperidinone **64** was deprotonated using LHMDS and the resultant enolate treated with carboxaldehyde **65** to give product **66**. This was then catalytically hydrogenated using palladium-black, forming a racemic product, which was resolved *via* chiral high-performance liquid chromatography to yield **67** as a single enantiomer in 36% yield (out of a maximum 50%). The target imidazolepropionic acid compound could then be synthesised, firstly *via* a ring-opening reaction facilitated by mild lithium hydroxide conditions, an acid hydrolysis and finally ion-exchange chromatography to give δ^2-amino acid **68** in ≥95% enantiomeric excess (Scheme 12).

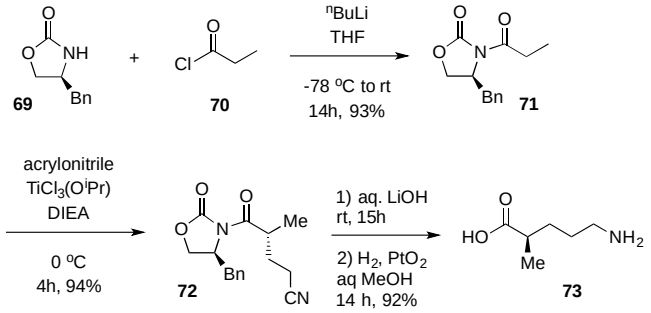


Scheme 12 : Bunnage and co-workers' resolution via chiral HPLC

4. Synthesis *via* Chiral Auxiliaries

Since their introduction in the 1970's, chiral auxiliaries have become a common method of controlling the stereochemical outcome of reactions and represent a viable option in the synthesis of extended amino acids. An early example of such an approach is given by Wilson and co-workers as part of their work

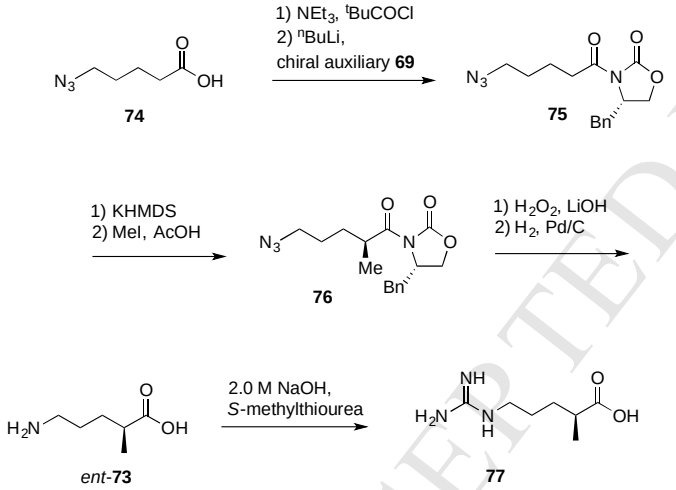
to synthesise peptide based inhibitors of interleukin-8 using an unnatural δ^2-amino acid within the sequence.[25] The Evans' chiral auxiliary (*S*)-4-benzyl 2-oxazolidinone was reacted with propionyl chloride to generate compound **71**. Acrylonitrile was then introduced in a stereoselective manner, forming Michael adduct **72**. Removal of the auxiliary and reduction of the nitrile under pressure, gave δ^2-amino acid **73** (Scheme 13). Mosberg also used this strategy in the synthesis of conformationally restricted peptidic analogs of the direct thrombin inhibitor FM 19.[26]



69 **70** **71** **72** **73**

Scheme 13 : Wilson's synthesis of δ-amino acid components of peptides aimed at inhibition of interleukin-8

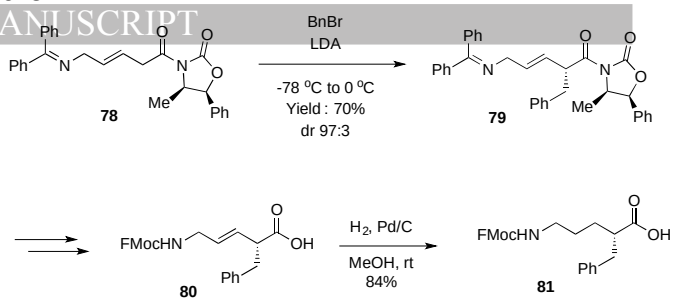
The enantiomer of compound **73** was required by the Dix group as isosteres of arginine and lysine for use as N-terminal capping residues.[27] Their synthesis of it only differed slightly in that they swapped the partner that was attached to the auxiliary.



74 **75** **76** *ent*-**73** **77**

Scheme 14: Dix's synthesis of a δ-amino acid *via* the use of a chiral auxiliary

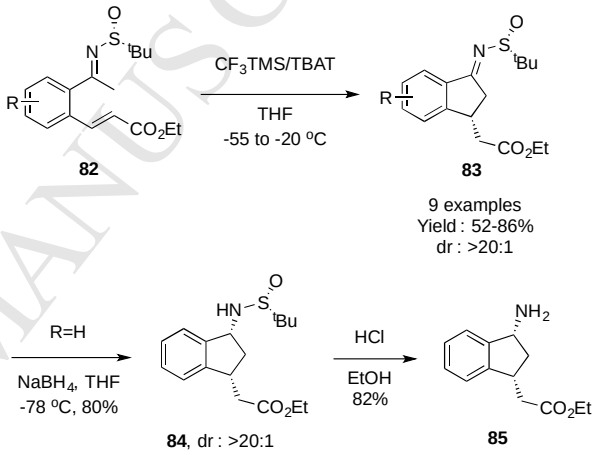
Linusson, Kihlberg and co-workers also utilized an auxiliary approach to their work described earlier in this review.[8b] Oxizolidinone **78** was alkylated with benzyl bromide in the presence of LDA to afford intermediate **79** in a 93:7 diastereomeric ratio – ultimately leading to the desired *N*-Fmoc protected δ^2-amino acid system (Scheme 15).



78 **79** **80** **81**

Scheme 15 : Kihlberg and Linusson's synthesis of a Gly-Phe isostere

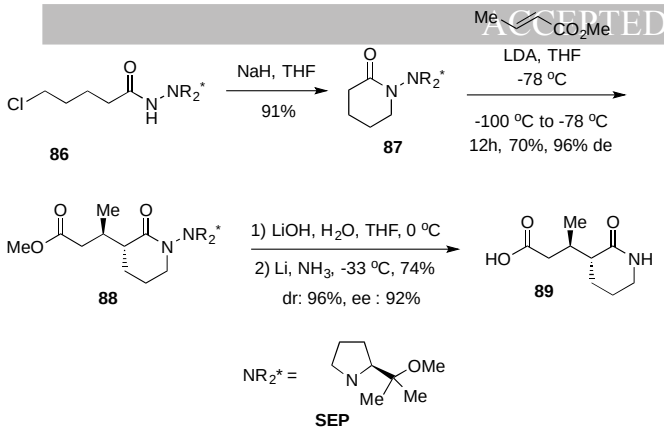
Fustero, Barrio and co-workers employed an *N*-sulfinyl imine auxiliary in their synthesis of a δ-amino acid indane.[28] Treatment of system **82** with CF_3TMS/TBAT gave the corresponding Michael adduct in good yield and excellent diastereoselectivity. Reduction of the *N*-sulfinyl imine bond of the product with sodium borohydride gave the *syn*-$\delta^{3,5}$-amino acid with similarly excellent diastereoselectivity. Removal of the auxiliary with HCl then gave the corresponding δ-aminoester in very good yield. (Scheme 16).



82 **83** **84**, dr : >20:1 **85**

Scheme 16 : Fustero and Barrio's synthesis of an indane δ-amino acid

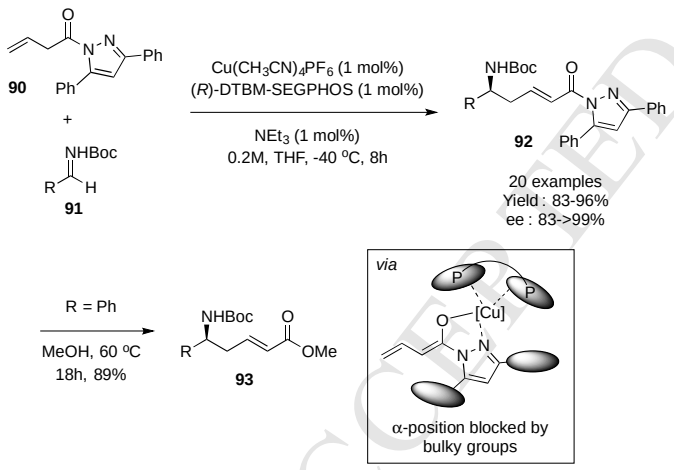
Finally, as δ-lactams can be hydrolysed to the corresponding δ-amino acid (as seen in Scheme 12), their asymmetric alkylation provides a potential route to enantiopure systems. A notable example of this is presented by Enders and co-workers using hydrazide chiral auxiliaries (Scheme 17).[29] Lactam **87** was formed by the cyclization of chloroalkano hydrazide **86**, which already bears the required chiral auxiliary (SEP shown at bottom of Scheme 17). This was then lithiated by treatment of LDA, followed by the addition of the appropriate propionic acid Michael acceptor to form the substituted lactam **88** to a high diastereomeric excess. Subsequent saponification of the ester group and removal of the chiral auxiliary gave the final lactam product **89** with an enantiomeric excess of 92%.



Scheme 17 : Enders use of a hydrazide auxiliary leads to a stereoselective reaction

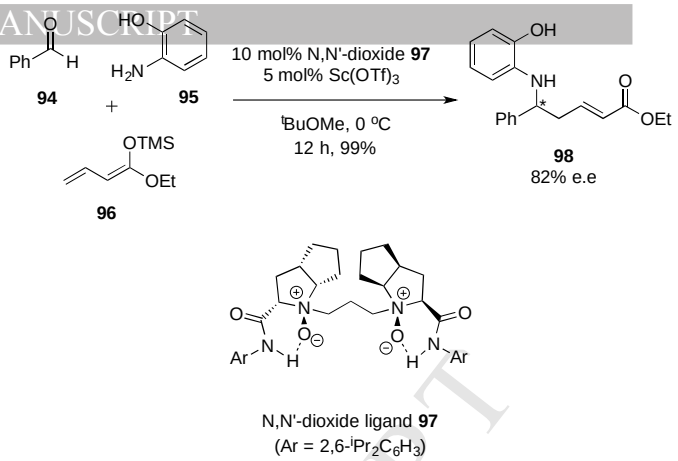
5. Synthesis *via* Enantioselective Catalytic Methods

Asymmetric catalysis - perhaps the most versatile and varied method of enantioselective synthesis - has been employed numerous times in the synthesis of enantiopure δ-amino acids and their analogues. Transition metal-based coordination complexes with chiral ligands are commonly utilised for this purpose, a wonderful recent example of which is given by Yin and co-workers in the direct asymmetric vinylogous Mannich-type reaction using a copper(I) complex (Scheme 18).[30] In this study a range of chiral phosphines were studied, but it was (*R*)-DTBM-SEGPHOS that was ultimately shown to be optimal. Although no real transition state is proposed, the bulky ligand and substituents of the pyrazole are thought to block addition of the acyl imine to the α-site (see box in scheme). Fascinatingly, this methodology was also able to be applied to the bisvinylogous Mannich-type reaction which led to ζ-amino acid precursors.



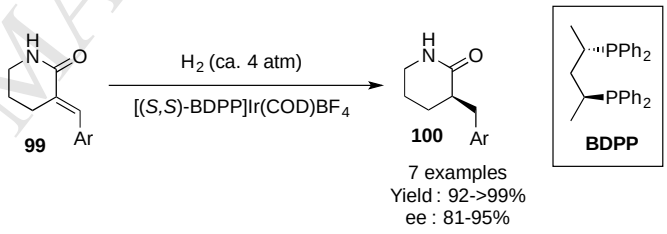
Scheme 18 : Yin and co-workers' direct asymmetric vinylogous Mannich-type reaction using a copper(I) complex

In a similar way, the Feng group at Sichuan University reported an asymmetric three-component vinylogous Mannich reaction catalysed by a chiral scandium complex.[31] Benzaldehyde **94**, aminophenol **94** and silyl dienol ether **96** were combined in the presence of $Sc(OTf)_3$ and the chiral ligand **97**, forming the δ-amino acid analogue **98**. A substrate scope was carried out, with a series of aromatic aldehydes investigated and the corresponding range of Mannich products obtained in comparative yields (≥ 90%) and enantiomeric excesses (≥ 80%).



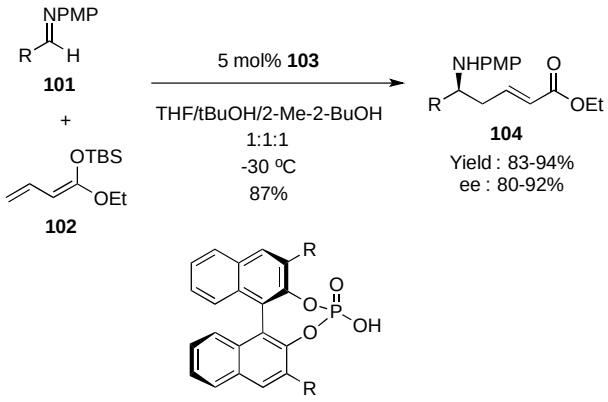
Scheme 19 : Feng's synthesis of δ[5]-amino acid analogues *via* a scandium catalysed Mannich reaction

Nugent and Yue developed an asymmetric hydrogenation of 3-alkylidenelactams – potential precursors to δ[2]-amino acids.[32] Improving upon work carried out by researchers at Merck,[33] the pair used an assortment of iridium, rhodium and ruthenium catalysts, screening a set of 32 chiral phosphine ligands. High conversions and enantioselectivities were found for the asymmetric hydrogenation of valerolactam **99** with a variety of metal/ligand combinations - the use of an Iridium catalyst bearing the BDPP ligand giving the best result (100% conversion, 91% e.e). Comparative results were then found for a range of 3-alkylidenelactam substrates, including both aromatic and aliphatic examples (Scheme 13).



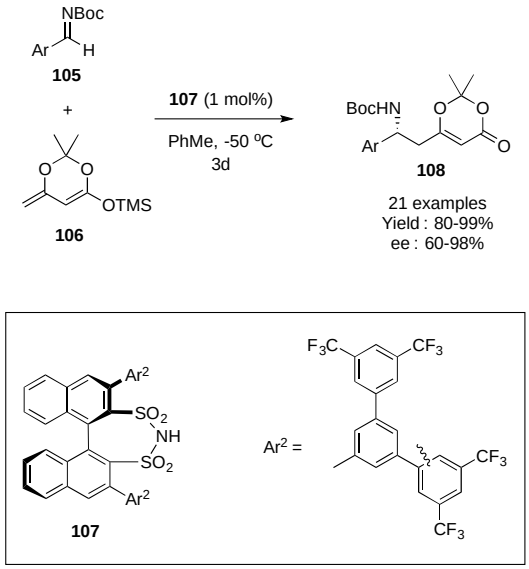
Scheme 20 : Yue and Nugent's synthesis of enantiopure δ[2]-lactams

Organocatalytic methods have also been employed in the synthesis of δ-amino acids. For example, Schneider and co-worker, reacted aldimine **101** with TBS-substituted dienolate **102** in the presence of the chiral phosphoric acid catalyst **103**, forming the Mannich product **104** in a high yield with good enantioselectivity.[34] The reaction proved viable for a range of aromatic aldimines (Scheme 21).



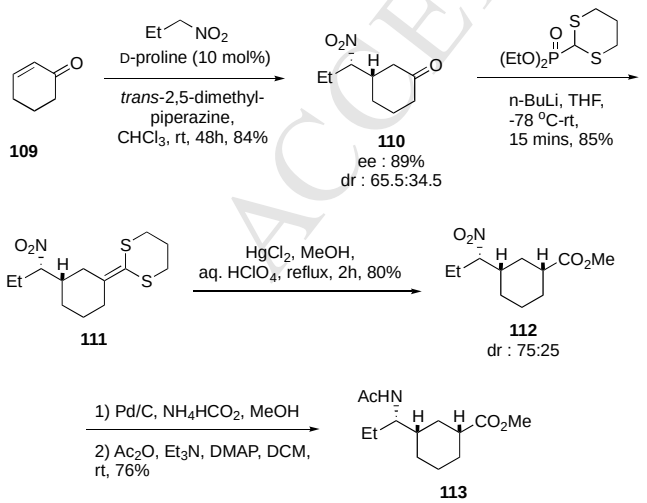
Scheme 21 : Schneider's synthesis of δ-amino acid analogues *via* a phosphoric acid catalysed Mannich reaction

List and co-workers have also developed a vinylogous Mukaiyama-Mannich process in the synthesis of δ-amino-β-ketoesters **108** using disulfonimide organocatalyst **107**.[35] A large range of *N*-Boc-imines **105** were utilized and the yields and selectivities were largely excellent (Scheme 22). However, the one nonaryl system that led to product suffered a much poorer selectivity.



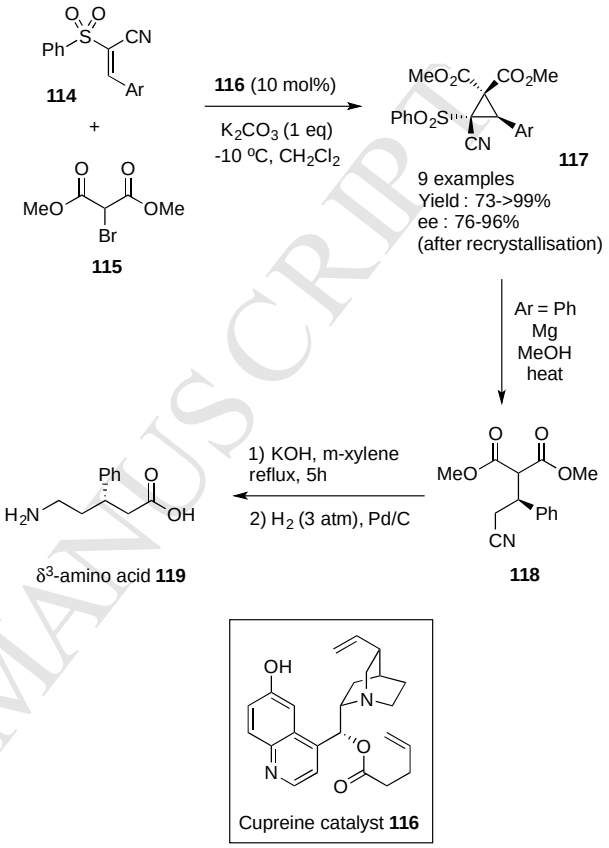
Scheme 22 : List's synthesis of δ^5-amino-β-ketoester derivatives by vinylogous Makaiyama-Mannich reaction

An approach which involves the organocatalytic formation of γ-amino acids followed by Wittig homologation in the generation of cyclic δ-Amino acid precursors as dipeptide mimcs is presented by Hanessian and co-workers,[36] with the ultimate aim of incorporating these into potentially therapeutic peptidomimetics. The group provide several synthetic routes in order to access the target compounds, one of which includes an organocatalytic component. Addition of 1-nitropropane to 2-cyclohexenone **109** in the presence of the amino acid D-proline gave adduct **110** with good enantioselectivity (89% e.e), but with poor diasteresoselectivity (~31%). With the required stereochemistry now implemented, the synthesis was continued and the target compound **113**, a $\delta^{2,4,5}$-amino acid formed in a total of 5 steps.



Scheme 23 : Hanessian's organocatalytic synthesis of δ-amino acid dipeptide mimetics

One last organocatalytic example comes from our own group in the asymmetric synthesis of δ^3-amino acids.[37] In this work, we developed a bifunctional cupreine catalyzed cyclopropanation between cyanosulfone **114** and bromomalonate system **115** (Scheme 24). Following the cyclopropane synthesis, a radical desulfonylation leads to cyclopropanation ring opening and ultimately to malonate **118**. Saponification followed by decarboxylation and reduction then led to the δ^3-amino acid. To the best of our knowledge this represents the most expedient asymmetric route to these δ^3-amino acid compounds currently known.



Scheme 24 : Our organocatalytic cyclopropanation route towards an acyclic δ^3-amino acid

Conclusions

Methods towards the synthesis of δ-amino acid systems are far less prevalent that those of shorter ones. Those that have been described tend to lean towards δ^2 or δ^5 systems. Nevertheless, various approaches from each class of asymmetric reaction are known and offer good scope depending on the target required. Of particular potential are the catalytic methods which show great promise towards the synthesis of δ^3 as well as δ^5 systems.

Acknowledgments

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